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EXAMINER	
LANDSMAN, ROBERT S	

ART UNIT	PAPER NUMBER
1647	15

DATE MAILED: 05/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/814,179	KIM ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears n the c ver sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *10-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,10,14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Formal Mattes

A. The Information Disclosure Statement, filed 8/29/01, has been entered into the record.

B. The Supplemental Information Disclosure Statement, filed 7/8/02, has been entered into the record.

C. The Supplemental Information Disclosure Statement, filed 3/6/03, has been entered into the record.

D. Claim 1-41 are pending in this application and were subject to restriction in Paper No. 7 dated 1/7/02. In Paper No. 9, filed 7/8/02, Applicants elected Group I, claims 1-16 and 41, without traverse. However, upon further consideration, the claims of Group I were subject to further restriction. Therefore, all pending claims, 1-41, were re-restricted in Paper No. 11, dated 10/7/02. In Paper No. 13, filed 3/6/03, Applicants elected Group I with traverse and argued that Groups I-IV should be recombined. Applicants also asked for the remaining Groups, separately, to be recombined. Upon further consideration, the Examiner has recombined Groups I-IV, claims 1-9 and 41. Therefore, Groups I-IV will be examined together. The issue regarding separately recombining the remaining Groups is, therefore, moot.

2. Specification

A. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The title is drawn toward a method of treating neurodegenerative diseases, whereas the claims are drawn toward a method of identifying agents which are useful in the treatments of a neurodegenerative disease.

3. Claim Objections

A. The syntax of claim 8 can be improved by amending the claim to recite "is useful in the treatment of."

B. Claim 41 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. No difference in these claims can be determined.

4. Claim Rejections - 35 USC § 112, first paragraph - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A. Claims 1-9 and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying compounds which potentiate CCE in cells which comprise various mutants, does not reasonably provide enablement for identifying agents useful in the treatment of any and all neurodegenerative diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

First, the breadth of these claims is excessive with regard to claiming a method of identifying compounds which are able to treat neurodegenerative diseases. These are "intended use" claims. Applicants intend to use the identified agents in the treatment of neurodegenerative diseases, including Alzheimer's disease and the other diseases recited in claim 3. Applicants have only demonstrated that presenilin and APP mutations are present in Alzheimer's disease (page 16, first full paragraph of the specification) and that presenilin mutations can decrease calcium influx (Figure 1). Applicants have not demonstrated that any other mutations, other than presenilin can alter calcium influx. Figures 6 and 7 discuss APP and TRP, but it is not clear from Figure 6, or from any of the Figures, how APP mutants, or APOE mutants, affect CCE. Furthermore, the claims are drawn to agents which potentiate CCE. However, Figure 7 shows that TRP, itself, potentiates CCE. Therefore, it is not clear how agents which potentiate CCE in TRP cells would aid in treating neurodegenerative diseases since these cells already have increased calcium flux.

Furthermore, Applicants claim that methods of potentiating CCE can be used to treat Alzheimer's disease, as well as, for example, Parkinson's, Huntington's and ALS, as well as any "neurodegenerative disease." The specification only teaches that Alzheimer's is associated with altered calcium flux. However, the specification provides no guidance or working examples of how to treat Alzheimer's, or

other neurodegenerative diseases, by potentiating CCE, nor does the specification teach what other neurodegenerative diseases, other than Alzheimer's, are even affected by potentiating CCE, nor would it be predictable as to what other diseases can be treated by potentiating CCE. Similarly, regarding claim 2, Applicants do not teach what other disease-linked mutations would lead to diseases which would be ameliorated by CCE potentiation, nor would it be predictable to the artisan what these mutations would be.

Therefore, the breadth of the claims is excessive with regard to intending to treat any and all neurodegenerative diseases with any and all disease-linked mutations. Applicants have only provided guidance and working examples showing that CCE is clearly altered in specific presenilin mutants. Furthermore, respectfully, Applicants have not demonstrated how these agents would be used to treat Alzheimer's disease or any other neurodegenerative disease, nor would it be predictable to the artisan how to do so. Therefore, the Examiner has concluded that undue experimentation would be required to practice the invention as claimed.

5. Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A. Claims 1-9 and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites a method of identifying an agent useful in the treatment of a neurodegenerative disease. However, it is not understood, respectfully, how identifying an agent which potentiates CCE can be guaranteed to be an agent which is useful in treating any, if not all, neurodegenerative diseases. This rejection can be overcome by amending the preamble to recite that the agent is potentially useful in the treatment of a neurodegenerative disease.

6. Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

A. Claims 1, 9 and 41 are rejected under 35 U.S.C. 102(a) as being anticipated by Birnbaumer et al. (US Patent No. 5,932,417 – reference AA1 on the Form PTO-1449 filed 8/29/01). The claims recite a method of identifying agents useful in the treatment of a neurodegenerative disease by assaying for agents which affect CCE, and wherein the cells overexpress TRP. Birnbaumer et al. teach a method of identifying compounds which may be useful in controlling CCE in mammalian cells (column 1, lines 20-24). Birnbaumer et al. also teach cells which overexpress TRP (column 2, lines 64-67; column 14, lines 57-58; column 15, lines 48 – column 16, lines 40, especially column 16, lines 34-40). The reference does not teach that CCE is linked to neurodegenerative diseases. Regardless, the assay (i.e. method steps) would be identical regardless of what the intention of the assay was for (Ex parte Novitski, 26 USPQ 1391).

B. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Buxbaum et al. (US Patent No. 5,538,983 - reference AB1 on the Form PTO-1449 filed 7/8/02). The claim recites a method of identifying agents useful in the treatment of a neurodegenerative disease by assaying for agents which

affect CCE by measuring CCE activities Buxbaum et al. teach a method of identifying compounds which may be useful in modulating calcium levels by detecting alterations in APP (column 2, lines 22-27).

C. Claims 1, 9 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Birnbaumer et al. (PNAS 93:15195-15202, 1996 - reference AT2 on the Form PTO-1449 filed 8/29/01). The claims recite a method of identifying agents useful in the treatment of a neurodegenerative disease by assaying for agents which affect CCE, and wherein the cells overexpress TRP. Birnbaumer et al. teach assays which increase CCE (i.e. CCE was measured). Birnbaumer also teach a method of identifying compounds which affect CCE (Figures 1 and 2). Birnbaumer et al. also teach cells which overexpress TRP (Abstract; Figures 1 and 2). Figure 9 teaches the activation of CCE by the agent, IP3. The reference does not teach that CCE is linked to neurodegenerative diseases. Regardless, the assay (i.e. method steps) would be identical regardless of what the intention of the assay was for (Ex parte Novitski, 26 USPQ 1391).

D. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Berridge. (Biochem. J. 312:1-11, 1995 - reference AR2 on the Form PTO-1449 filed 8/29/01). The claims recite a method of identifying agents useful in the treatment of a neurodegenerative disease by assaying for agents which affect CCE. Berridge teaches an assay which measures CCE in the presence of the agent, thapsigargin (Figure 3). The reference does not teach that CCE is linked to neurodegenerative diseases. Regardless, the assay (i.e. method steps) would be identical regardless of what the intention of the assay was for (Ex parte Novitski, 26 USPQ 1391).

E. Claims 1, 9 and 41 are rejected under 35 U.S.C. 102(e) as being anticipated by Birnbaumer et al. (US Patent No. 5,932,417). The claims recite a method of identifying agents useful in the treatment of a neurodegenerative disease by assaying for agents which affect CCE, and wherein the cells overexpress TRP. Birnbaumer et al. teach a method of identifying compounds which may be useful in controlling CCE in mammalian cells (column 1, lines 20-24). Birnbaumer et al. also teach cells which overexpress TRP (column 2, lines 64-67; column 14, lines 57-58; column 15, lines 48 – column 16, lines 40, especially column 16, lines 34-40). The reference does not teach that CCE is linked to neurodegenerative diseases. Regardless, the assay (i.e. method steps) would be identical regardless of what the intention of the assay was for (Ex parte Novitski, 26 USPQ 1391).

7. Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

A. Claims 1-4, 7-9 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (reference AR12 on the Form PTO-1449, filed 8/29/01) in view of Birnbaumer et al. (PNAS).

The claims recite a method of identifying agents useful in the treatment of a neurodegenerative disease, including Alzheimer's disease, by assaying for agents which affect CCE, and wherein the cells overexpress TRP. The claims also recite that the cells have a disease-linked mutation. Kim et al. teach that perturbed calcium homeostasis is one of the characteristic molecular phenotypes associated with presenilin FAD mutations and that cells expressing the N141I FAD mutant of PS2 exhibited an increased tendency to form aggregates. Kim et al. also teach that when CCE was induced, cells expressing mutant PS2 exhibited a reduced, but more sustained increase in cytosolic free calcium, which could be abolished by the CCE antagonist, SKF96365, indicating that CCE is altered by the N141I mutation. Therefore, Kim et al conclude that reduced CCE may be an important molecular consequence associated with FAD-lined neurodegeneration.

Kim et al. do not teach screening methods to identify agents which affect CCE. However, Birnbaumer et al. do teach a method of screening compounds for controlling CCE. The teachings of Birnbaumer are recited in the above rejection under 35 USC 102.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the present invention to have screened cells for agents useful in the treatment of neurodegenerative diseases such as Alzheimer's disease wherein the cells have presenilin mutations since it was known in the art that disease-linked presenilin mutations, as seen in neurodegenerative diseases including Alzheimer's, were associated with altered CCE. Therefore, identifying agents which could affect CCE would be an important step in attempting to treat Alzheimer's, or other neurodegenerative diseases which involve CCE.

B. Claims 1 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (reference AR on the Form PTO-1449, filed 8/29/01) in view of Birnbaumer et al. (PNAS) and further in view of Gibson (reference AR8 on the Form PTO-1449, filed 8/29/01).

The claims recite a method of identifying agents useful in the treatment of a neurodegenerative disease, including Alzheimer's disease, by assaying for agents which affect CCE and wherein the cell contains an APP mutant. The teachings of Kim and Birnbaumer are taught in the above rejection under 35 USC 103. Neither Kim nor Birnbaumer teach APP mutants. However, Gibson do teach that APP mutations do occur in Alzheimer's disease and that bombesin-induced elevations in calcium in APP670/671 mutation-bearing cell lines were reduced by 40% (Abstract). Gibson also teach that altered regulation of internal calcium stores is common to all AD lines.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the present invention to have screened cells for agents useful in the treatment of neurodegenerative diseases such as Alzheimer's disease wherein the cells have APP mutations since it was known in the art that APP mutations, which occur in Alzheimer's, lead to the accumulation of Aβ peptide, which is believed to be an early morphological event in AD pathology preceeding neurodegeneration (Introduction). Therefore, since aggregation of mutant proteins has been taught by Kim et al. to be involved in Alzheimer's, and CCE plays a role in this aggregation and, therefore, the possible onset of AD, identifying agents which could affect CCE (i.e. affect calcium regulation) would be an important step in attempting to treat Alzheimer's, or other neurodegenerative diseases which involve CCE in which the aggregation of other proteins involved in AD is known to occur, such as APP mutants.

C. Claims 1 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (reference AR on the Form PTO-1449, filed 8/29/01) in view of Birnbaumer et al. (PNAS) and further in view of Maslian et al. (Prog. Neurobiol. 50:493-503, 1996).

The claims recite a method of identifying agents useful in the treatment of a neurodegenerative disease, including Alzheimer's disease, by assaying for agents which affect CCE and wherein the cell contains an APP mutant. The teachings of Kim and Birnbaumer are taught in the above rejection under 35 USC 103. Neither Kim nor Birnbaumer teach APOE mutants. However, Maslian do teach that APOE regulates levels of intracellular calcium (Abstract) and that abnormal APOE (e.g. mutation) does occur in Alzheimer's disease (Abstract and page 498, right column).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the present invention to have screened cells for agents useful in the treatment of neurodegenerative diseases such as

Alzheimer's disease wherein the cells have altered APOE (e.g. mutation) since it was known in the art that altered APOE function occurs in Alzheimer's patients and that APOE is involved in calcium regulation. Therefore, identifying agents which could affect CCE (i.e. affect calcium regulation) would be an important step in attempting to treat Alzheimer's, or other neurodegenerative diseases which involve calcium regulation, for which CCE is a part.

8. Conclusion

A. No claim is allowable.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
May 09, 2003

ROBERT LANDSMAN
PATENT EXAMINER